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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,527	07/10/2006	Jean-Philippe Girard	CNRS.001APC	2903

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/539,527	GIRARD ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2009 and 13 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25,26,28,32 and 127* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25,26,28,32 and 127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-8-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 8, 2009 has been entered.

Status of Claims

Claims 23, 25-26, 28, 32, and 127 are currently pending and under examination on the merits in the instant case.

Response to Arguments

Applicant's arguments with respect to claims 23-26, 28, 30-35, 37, and 127-129 filed with the RCE have been considered but are moot in view of the new ground(s) of rejection. See below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 8, 2009 is being considered by the examiner except Zabel et al. (1991), whose copy is illegible. Further, WO 90/11354, WO 93/01288, WO 95/01987, and WO 97/05277 are considered only insofar as their

English titles and abstracts, and Cwirla et al. reference (1990) is considered only insofar as pages 6381-6382, which are the only pages submitted by applicant.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/435,827, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. It is found that the provisional application merely provides the term "small interfering RNAs" in one paragraph such that they can be used to inhibit the function of NF-HEV or to reduce the development of HEV-like vessels. See page 8, first paragraph. Except the single paragraph in the 100-page long specification of the provisional application, there is nothing whatsoever that provides "adequate" support/enablement for the claimed chronic inflammation treatment methods comprising the claimed method steps in the

manner provided by the first paragraph of 35 U.S.C. 112. As applicant must be aware, the provisional application is devoted to a prophetic disclosure pertaining to NF-HEV antibody production and related aspects thereof and a prophetic disclosure of NF-HEV inhibitors in treatment methods. There is nothing whatsoever that indicates that the inventors were in possession of the claimed siRNA-based therapeutic methods or that the inventors provided an enabling disclosure or sufficient, useful, specific teachings pertaining to the claimed siRNA-based treatment methods comprising the method steps recited in the instant application (e.g., identifying a subject having symptoms of chronic inflammation condition; administering an siRNA that reduces pro-inflammatory chemokine; reducing NF-HEV by reducing the activity of a pro-inflammatory cytokine; siRNA is targeted against the nucleotide sequence encoding amino acids 1-65 of SEQ ID NO:4). Hence, the benefit of the 60/435,827 filing date for claims 23, 25-26, 28, 32, and 127 is denied, and therefore, the filing date of PCT/IB03/06477 (December 18, 2003) will be the effective filing date for claims 23, 25-26, 28, 32, and 127. If applicant believes that 60/435,827 provides adequate support and enablement for the claimed subject in the instant application in the manner provided by the first paragraph of 35 U.S.C. 112, applicant is advised to point out particulars in response to this Office action.

Claim Objections

Claims 23, 25, 26, 32, and 127 are objected to because of the following informalities: The claims recite an acronym "NF-HEV". The abbreviated term may mean different subject matter than the subject matter intended by applicant. Hence, it is suggested the acronym be fully spelled out for at least its first occurrence. Further, the specification does not explicitly provide

the definition for the acronym. For examination purpose, the term "NF-HEV" will be interpreted to mean "nuclear factor-high endothelial venules", which encodes a protein product of 270 amino acids of SEQ ID NO:4 based on paragraphs 0169-0172. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 depends from claim 23, wherein claim 23 recites an active method of step of administering an siRNA targeted to SEQ ID NO:1, wherein the active method step reduces the expression level and activity of NF-HEV polypeptide encoded by SEQ ID NO:1. Claim 32, however, recites that the level or activity of NF-HEV polypeptide is reduced "by reducing the activity or level of a pro-inflammatory cytokine." See lines 2-3 of claim 32. Hence, the active method step (reducing NF-HEV polypeptide by reducing pro-inflammatory cytokine level) recited in claim 32 is different from and conflicting with the active method step (reducing NF-HEV polypeptide by reducing the level of NF-HEV polypeptide with an siRNA) recited in claim 23, thereby rendering claim 32 indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over King et al. (US 2002/0131971 A1) in view of Lewis et al. (US 2003/0143204 A1).

King et al. teach that one can induce or stimulate immune responses in a patient by expressing a polynucleotide of SEQ ID NO:1879 that encodes human DSV27-related protein. It is noted that the entire SEQ ID NO:1879 (574 nucleotides in length) is 99% identical to nucleotides 1659-2232 of SEQ ID NO:1 in which nucleotide positions 8 and 275 of SEQ ID NO:1879 are different from nucleotides of SEQ ID NO:1 of the instant application. See claims 1, 9, 11-12; Table 4 at page 74. King et al. do not teach treating an inflammation condition in a subject by inhibiting immune responses in the subject with an siRNA that decreases SEQ ID NO:1879 that encodes DSV27-related protein.

Lewis et al. teach that one can make a target-specific siRNA compound and use it to inhibit target expression/activity in a mammal for therapeutic applications that involve inhibiting immune responses, thereby alleviating inflammation and treating inflammatory diseases in the mammal. See paragraphs 0008-0009, 0018-0019, 0033-0037, 0042-0045, 0197.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit the activity of SEQ ID NO:1879 of King et al. with an siRNA in a subject to inhibit or down-regulate immune responses in the subject.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to alleviate inflammatory-related conditions because SEQ ID NO:1879 encoding human DVS27-related protein was known to stimulate/induce immune responses in a patient as taught by King et al., and because siRNAs were known to inhibit target expression/activity in a sequence-specific manner and thus were known to be useful in therapeutic applications for treating inflammatory diseases as taught by Lewis et al. Since the immune-stimulatory nucleotide sequence of SEQ ID NO:1879 of King et al. is highly homologous to a fragment of SEQ ID NO:1 claimed to be targeted by an siRNA, the siRNA targeted to any portion of SEQ ID NO:1879 of King et al. would necessarily reduce the immune-stimulatory activity of SEQ ID NO:1 of the instant application, thereby treating a condition associated with inflammation in a subject. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 23, 25, and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipman (*Current Rheumatology Reports,* 2001, 3:513-519) in view of Woolf et al. (US 2007/0015145 A1, citation of record) and Elbashir et al. (*Methods,* 2002, 26:199-213).

Lipman teaches that chronic pain is one of the symptoms of osteoarthritis, a chronic inflammation condition, and therefore patients having osteoarthritis are recommended to take an anti-inflammatory drug and an analgesic drug such as a non-steroidal anti-inflammatory drug (NASID), which is the analgesic/anti-inflammatory agent. Lipman also teaches that treatment of pain in osteoarthritis may need other types of therapies for better pain management. See the entire reference. Lipman does not teach that one can ameliorate chronic pain, a symptom of osteoarthritis, with an siRNA targeted to a gene encoding SEQ ID NO:4.

Woolf et al. teach that there is an art-recognized need to identify therapeutic strategies other than non-steroidal anti-inflammatory drugs (NSAIDS) for more effective pain management. Woof et al. teach that one can treat chronic pain in a subject by administering an siRNA targeted to a polynucleotide of SEQ ID NO:11450 that is differentially over-expressed in the subject having chronic pain instead of administering NSAIDS, wherein the polynucleotide of 2645 nucleotides in length of SEQ ID NO:11450 is identical to the 2465 nucleotides of SEQ ID NO:1 of the instant application and that SEQ ID NO:11450 encodes SEQ ID NO:11451, whose 270 amino acids are identical to the 270 amino acids of SEQ ID NO:4 of the instant application. They teach that therapeutic siRNA molecules base pair with the endogenous transcripts, thereby inhibiting translation of the target mRNA. See paragraphs 0003-0005; 0015; 0077-0078; 0081; 0283-0287; 0376; claims 44-45.

Elbashir et al. provide guidelines one can follow to design effective siRNA molecules such that one selects an "5'-AA(N19)UU" or "5'-AA(N21)" sequence motif having about 32-79% GC content within the coding region of a target mRNA beginning from about 50-100 nucleotides downstream of the start codon. They experimentally demonstrate the efficacy of their siRNA selection method by making and testing a number of different target-specific siRNAs. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat chronic pain in a patient having osteoarthritis, a chronic inflammation condition, by reducing the activity of SEQ ID NO:11450 of Woolf et al., which is over-expressed in the subject having chronic pain, by administering an siRNA targeted to a portion of SEQ ID NO:11450 of Woolf et al., wherein the targeted portion encodes any portion of amino acids 1-65 of SEQ ID NO:11451 of Woolf et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to more effectively manage the painful symptoms in a patient having osteoarthritis, because the need to find a more effective treatment strategy for osteoarthritis-related pain other than NASIDS was recognized in the art as taught by Woolf et al. and Lipman, wherein NASIDS agents are the primary approach for ameliorating pain associated with osteoarthritis as taught by Lipman, and because an siRNA-based therapeutic strategy that inhibits the function/expression of SEQ ID NO:11450 encoding SEQ ID NO:11451 of Woolf et al. was suggested as an alternative pain management and treatment method, wherein the nucleotide sequence of SEQ ID NO:11450 of Woolf et al. is found to be identical to that of SEQ ID NO:1 of the instant application and the amino acid sequence of SEQ ID NO:11451 of Woolf et al. is

identical to that of SEQ ID NO:4 of the instant application. Since the goal as well as the essential method steps of ameliorating symptoms associated with a chronic inflammation condition with an siRNA targeted to SEQ ID NO:11450 of Woolf et al. (identical to SEQ ID NO:1 claimed in the instant case) were known in the art, and since one of ordinary skill in the art would have been expected to reasonably make an siRNA targeted to a portion of the coding region (e.g., nucleotides 122-142 of AB024518 encoding amino acids 36-41 of BAA75892, wherein the selected target nucleotide sequence satisfies the "5'-AA(N21)" sequence motif rule and the GC content rule), one of ordinary skill in the art would have reasonably reduced the inflammatory activity of SEQ ID NO:11450 or SEQ ID NO:11451 of Woolf et al. in a subject by administering an siRNA targeted to a portion of the nucleotide sequence encoding amino acids 1-65 of SEQ ID NO:4 as claimed in the instant case. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time the application was filed.

Claims 23, 25-26, 28, 32, and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onda et al. (*Journal of Cerebral Blood Flow & Metabolism,* 1999, 19:1279-1288) in view of GenBank accession Nos. AB024518 and BAA75892 (both submitted in the Onda et al. reference and deposited in the NCBI database on March 10, 1999; see the attached citations), Lewis et al. (US 2003/0143204 A1), and Elbashir et al. (*Methods,* 2002, 26:199-213).

Onda et al. teach that DVS27 and other inflammation-related genes are highly upregulated in the vasospastic arteries of canine two-hemorrhage models, thereby suggesting that inflammatory reaction may be involved in the pathogenesis of cerebral vasospasm or cerebral ischemia. They teach that the first identified canine DVS27 nucleotide sequence isolated from a

dog is deposited in GenBank with the accession No. AB024517. They also disclose the canine composite nucleotide sequence of DVS27 in Figure 5. They teach that their experimental results suggest that human DVS27 expression is highly increased in human vascular smooth muscle cells in response to inflammatory reactions induced by IL-1α and IL-1β . See page 1284. They suggest that "the DVS 27 gene was found to encode a nuclear protein that could be involved in inflammatory events." See page 1287. Onda et al. do not teach inhibiting the inflammatory activity of DSV27 with a DSV27-specific siRNA in a subject having chronic inflammation to ameliorate the symptoms of the inflammation in the subject.

In addition to the canine DVS27 nucleotide sequence disclosed in the Onda et al. reference, the human DVS27 nucleotide sequence encoding a protein of 270 amino acids identical to the 270 amino acids of SEQ ID NO:4 of the instant application was also publicly available as Onda et al. deposited the nucleotide sequence encoding the human homolog of the canine DVS27 as GenBank accession No. AB024518 in the NCBI database on March 10, 1999 along with the human amino acid sequence as GenBank accession No. BAA75892. See the attached citations.

Lewis et al. teach that one can make a target-specific siRNA compound targeted to the coding region of a target mRNA sequence and use it to inhibit target expression/activity in a mammal for therapeutic applications that involve inhibiting immune responses, thereby alleviating inflammation and treating inflammatory diseases in the mammal. See paragraphs 0008-0009, 0018-0019, 0033-0037, 0042-0045, 0197.

Elbashir et al. provide guidelines one can follow to design effective siRNA molecules such that one selects an "5'-AA(N19)UU" or "5'-AA(N21)" sequence motif having about 32-79%

GC content within the coding region of a target mRNA beginning from about 50-100 nucleotides downstream of the start codon. They experimentally demonstrate the efficacy of their siRNA selection method by making and testing a number of different target-specific siRNAs. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit human DVS27-induced inflammatory reactions in a subject having upregulated, harmful inflammatory responses or an inflammatory disease with an siRNA targeted to the human DVS27 nucleotide sequence.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to ameliorate inflammation-associated clinical symptoms in a subject because human DVS27 mRNA expression was known to be upregulated in human cells in response to inflammatory cytokines IL-1α and IL-1β and was suggested to encode a nuclear protein involved in inflammatory events as taught by Onda et al., and because the human DVS27 mRNA sequence was publicly available in the art as deposited by Onda et al. on March 10, 1999 in the publicly accessible NCBI database, and because siRNA-based therapy was suggested to be useful for treating inflammatory diseases when the target sequence and its functional role in inducing immune responses are known as taught by Lewis et al. Since the nexus between human DVS27 expression level and increased inflammatory/immune responses in a human cell was reasonably established in the art, and since target mRNA sequence-specific siRNA-based therapeutic approach was a known inflammatory disease treatment method recognized in the art as taught by Lewis et al., and since the instantly claimed target sequence was already isolated and identified by other researchers in the art in the year of 1999, one of ordinary skill in the art

would have had a reasonable expectation of success in arriving at the claimed invention prior to the filing of the instant application. Further, since it was explicitly suggested that the human DVS27 is involved in promoting inflammatory events, one of ordinary skill in the art would have necessarily reduced the activity of inflammatory chemokines in the cells of a subject with an siRNA targeted to the coding region of human DVS27 of Onda et al. with a reasonable expectation of success, wherein one of ordinary skill in the art would have reasonably made an siRNA targeted to a portion of the coding region (e.g., nucleotides 122-142 of AB024518 encoding amino acids 36-41 of BAA75892, wherein the selected target nucleotide sequence satisfies the "5'-AA(N21)" sequence motif rule and the GC content rule), and as such, one of ordinary skill in the art would have reasonably reduced inflammatory/immune responses in a subject by administering an siRNA targeted to a portion of the nucleotide sequence encoding amino acids 1-65 of SEQ ID NO:4 as claimed in the instant case. Further, since DVS27 expression and inflammatory activity were known to be induced by pro-inflammatory cytokines such as IL-1α and IL-1β, one of ordinary skill in the art would have reasonably reduced the level/activity of human DVS27 by reducing the activity/level of IL-1α and IL-1β as claimed in claim 32. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore (Acting SPE) can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

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